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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/066,521	01/31/2002	John Bertin	07334-334001	3688

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EXAMINER	
CANELLA, KAREN A	
ART UNIT	PAPER NUMBER
1643	

DATE MAILED: 07/27/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/066,521	BERTIN ET AL.	
	Examiner	Art Unit	
	Karen A. Canella	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4-7,11,21-27,30-35 and 37-44* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *1,4,6,7,11,21 and 34* is/are allowed.

6)☒ Claim(s) *1; 5, 22-27, 30-33, 35, 37-44* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claim 36 has been canceled. Claims 30-33 have been amended. Claims 1, 4-7, 11, 21-27, 30-35 and 37-44 are pending and under consideration.

2. Sections of title 35, U.S. code not found in this action can be found in a previous action.

3. Claims 5, 22-27, 30-33, 35, and 37-44 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 30-34 have been amended to specify a fusion protein with a heterologus peptide. The specification as filed states that fusion proteins with all or part of the disclosed pyrins are part of the invention, this does not provide support for the instant claims that require fusion proteins with specific residues of SEQ ID NO:6

Claim5 was amended with the response filed November 1, 2004 to incorporate the limitation of encoding a polypeptide that stimulates apoptosis. The specification as filed contemplates primers and oligonucleotides which hybridize under the recited conditions, but does not provide support for a nucleotide sequence which encodes a polypeptide that stimulates apoptosis which hybridizes under the conditions as stated.

Claims 22 and 25 were amended with the response filed November 1, 2004 to incorporate the limitation of the polypeptide stimulating apoptosis. The specification as filed contemplates polypeptides having 85% identity to SEQ ID NO:5 or 6, but does not provide support for said variant polypeptides having the ability to stimulate apoptosis.

4. The rejection of claims 5, 22-27, 30-33, 35-44 under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for how to make and use a polynucleotide encoding the polypeptide of SEQ ID NO:6, does not reasonably provide enablement for polynucleotide encoding a polypeptide having 85%, 95% or 98% sequence identity to SEQ ID NO:6 or a polynucleotide encoding a polypeptide which minimally comprise residues 1-91, 188-

506 or 688-1056 of SEQ ID NO:6 or a polynucleotide which hybridizes to SEQ ID NO:5 is maintained for reasons of record. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claims 5, 22 and 25 have been amended to incorporate the limitation "polypeptide stimulates apoptosis". The specification states on page 3, lines 23-26 that PYRIN-5 has a nucleotide binding site domain which is present in a number of proteins that transmits signals which activate apoptotic and inflammatory pathways in response to stress and other stimuli; the specification states on page 3, lines 27-29 that PYRIN-5 has a leucine rich domain, which is a domain present in a number of proteins involved in apoptotic pathways. The specification suggests on page 5, lines 11-17 that the LRR domain of PYRIN-5 interacts with an upstream signaling molecule that is associated with stress, infections and/or inflammation and that this interaction results in a conformational change of the pyrin domain. The specification suggests on page 5, lines 17-21, that the exposed pyrin domain then interacts with a downstream signaling molecule(s) to transmit a stress-related apoptotic or inflammatory signal. The specification does not identify the upstream molecule or molecules that bind to the LRR domain of PYRIN-5 which would serve to expose the pyrin domain or the downstream signaling molecules which interact with the exposed pyrin domain. One of skill in the art would conclude that PRYIN-5 would not provide an apoptotic signal without the binding to said molecule or molecules to the LRR domain and interaction with the appropriate downstream signaling molecule which would actually provide an effective apoptotic signal. The specification does not teach a cell type that would be expected to provide the appropriate upstream molecule or molecules which would interact with the LRR domain of PYRIN-5, therefore the transduction of any given cell with a nucleic acid encoding a protein which is 85%, 95% or 98% identical to SEQ ID NO:6 would not guarantee that said protein would encounter the necessary molecule or molecule which would bind the LRR domain of the variant, alter the conformation of the pyrin domain in such a way as to enable interaction with the downstream signaling molecule(s) in order to effect apoptosis necessary to fulfill the requirements of claims 5, 22-27.

Claims 30-33 are drawn to an isolated nucleic acid molecule that encodes a polypeptide comprising residues 1-91, 188-506 or 688-1056 of SEQ ID NO:6. The specification teaches that

residues 1-91 of SEQ ID NO:6 are the pyrin domain, residues 188-506 are the NBS domain and residues 688-1056 are the LRR domain. The specification provides no teachings as to the structural variations which could be tolerated by PYRIN-5 wherein said structural variations would result in a variant molecule having the ability to expose the pyrin domain within the molecule upon binding of a upstream signaling molecule to the LRR domain. The claim reads on a protein which minimally comprises the LRR domain without the pyrin or NBS domains. The specification has not taught the upstream signaling molecule which would bind to the LRR domain or the cell type which would express such upstream molecule or molecules, therefore one of skill in the art, although able to make a protein which minimally comprises the LRR domain would not be able to use the resultant protein, for instance, in the blocking of such an upstream signal. The claims read on a protein which minimally comprise the pyrin domain. The specification has not the downstream signaling molecule which interacts with said pyrin domain or a cell type would express the downstream signaling molecule necessary to transmit the apoptotic signal. The claims read on a protein which minimally comprise the NBS domain. The specification teaches on page 5, lines 17-21 that the conformational change induced by the binding of an upstream signaling molecule or molecules is dependent upon hydrolysis of a nucleotide phosphate bound to the NBS domain. The specification has not a use for such a protein that does not comprise the LRR domain and the pyrin domain. Further, the specification has not taught the physical requirements of the interaction between the LRR domain and the NBS domain which potentate the exposure of the pyrin domain. The claims read on a protein in which the residues were directly fused to each other, such as residue 91 followed by residue 188, where residue 688 is immediately after residue 506. Such a conformation would dramatically alter the interaction between the domains because the relative position of the domains in space would not resemble the relative positions of the domains in SEQ ID NO:6. It would not be expected that such a protein would be able to function as SEQ ID NO:6. For example it is well known in the art that proteins are folded 3-dimensional structures, the function and stability of which are directly related to a specific conformation (Mathews and Van Holde, Biochemistry, 1996, pp. 165-171). In any given protein, amino acids distant from one another in the primary sequence may be closely located in the folded, 3-dimensional structure (Mathews and Van Holde, Biochemistry, 1996, pp. 166, figure 6.1). The specific conformation

of a protein results from non-covalent interactions between amino acids, beyond what is dictated by the primary amino acid sequence. A different amino acid sequence surrounding the claimed domains of SEQ ID NO:6 can potentially radically alter the three dimensional structural environment in which the given domain is located (Matthews, B. "Genetic and Structural Analysis of the Protein Stability Problem", In: Perspectives in Biochemistry, Neurath Ed., 1989) thus, the consequences of the altered sequence environment cannot be predicted. It is noted that the specification does not teach a use for such a protein which would not mediate apoptosis in the same manner as SEQ ID NO:6. Due to these reasons, one of skill in the art would be forced into undue experimentation in order to make and use the broadly claimed nucleic acids which minimally encode the isolated domains of SEQ ID NO:6.

5. Applicant has provided the Declaration of Frederick Lo which asserts that Pyrin-5 induces apoptosis in HeLa cells, NIH-3T3 cells and neurons (page 2, section 5 of the Declaration). However, the substance of the declaration, that Pyrin-5 can induce apoptosis in HeLa cells, NIH-3T3 cells and neurons cells when supplied by a recombinant expression vector is not part of the specification as filed. Therefore these teachigns as applied to the screening of varaints which differ in structure from SEQ ID NO:5 or 6 to identify said varaints that can function in a pro-apoptoic manner was not enabled as of the filing date. The Declaration does not address the tolerance of Pyrin-5 to structural alterations which would not affect the ability of the varaint Pyrin to stimuyate apoptosis.

Applicant argues that the specification teaches that "modulators of Pyrin-5 expression of activity can be used to treat disorders assoicated with inappropriate apoptosis, including neurological disorders assoicate with neuronal apoptosis". This statement has been considered but not found to be persuasive. The cited text clearly refers to "modulators" of Pyrin-5, such as antagonists, and not Pyrin-5 itself. Further, one of skill in the art would conlude that neurological disorders assoicated with neuronal apoptosis include disorders where there was inappropirate neuronal apoptotic actvity, such as the degeneration of the dopaminergic nigrostriatal neuron in Parkinson's disease (abstract of Ziv, et al, Advances in Research on Neurodegeneration, 1997, Vol. 3-4, pp. 195-202). Thus, given the teachings of the specification, one of skill in the art would conclude that administration of an antagonist of Pyrin-5 would

prevent the induction of apoptosis in neurons. There is no direct nexus between these teachings and the induction of apoptosis in HeLa, NIH-3T3 or neuronal cells by supplying a recombinat vector encoding Pyrin-5.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen A. Canella whose telephone number is (571)272-0828. The examiner can normally be reached on 11 am to 10 pm, except Wed, Fri.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on (571)272-0832. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Karen A. Canella, Ph.D.
7/25/2005

Karen A. Canella

KAREN A. CANELLA PH.D
PRIMARY EXAMINER